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14AUG02 E740732-2 D01631
P01/7700 0.00-0218811.8

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14 AUG 2002

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1. Your reference

44862/JMD/NT

2. Patent application number
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0218811.8

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

CeNeS Limited
Compass House
Vision Park
Chivers Way
Histon
Cambridge
CB4 4ZR

Patents ADP number *(if you know it)*

7313877002

If the applicant is a corporate body, give the country/state of incorporation

United Kingdom

4. Title of the invention

Salts of Morphine-6-Glucuronide

5. Full name, address and postcode in the United Kingdom to which all correspondence relating to this form and translation should be sent

Reddie & Grose
16 Theobalds Road
LONDON
WC1X 8PL

Patents ADP number *(if you know it)*

91001 ✓

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application *(If you know it)*	Date of filing *(day/month/year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day/month/year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
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Description	6
Claim(s)	1
Abstract	0
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Priority documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	0
Request for preliminary examination and search *(Patents Form 9/77)*	0
Request for substantive examination *(Patents Form 10/77)*	0
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature: Reddie & Grose

Date: 12 August 2002

12. Name and daytime telephone number of person to contact in the United Kingdom: J M DAVIES 01223 360350

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44862.GB01

Salt of Morphine-6-Glucuronide

This invention relates to a salt of morphine-6-β-D-glucuronide (M6G; see Figure 1) with improved stability, and to use of the salt as a medicament, in particular as an analgesic.

M6G is a metabolite of morphine which is known to be a more powerful analgesic than morphine itself and yet has fewer side effects. Methods of preparation of M6G are described in WO 93/03051, WO 93/05057, WO 99/58545 and WO 99/38876.

Whilst M6G base is stable when stored at -20°C, it does degrade when stored at room temperature. This degradation is not only noted by an increase in detectable degradation products, but also by a marked colour change of the compound. This will limit the shelf life of M6G base at ambient temperature.

It has now been found that the hydrobromide salt of M6G (M6G.HBr) is surprisingly stable compared to other M6G salts, in particular the hydrochloride (M6G.HCl) and sulphate (M6G.H_2SO_4) salts. M6G.HBr showed a very limited amount of degradation and no discolouration after storage at room temperature for six years (see Example 1 below).

According to the invention there is provided a hydrobromide salt of M6G (M6G.HBr). A method of preparation of M6G.HBr is described in Example 2 below.

M6G.HBr may be used as a medicament, in particular as an analgesic. Examples are for the treatment of moderate to severe, acute and chronic nocicepive pain (such as post-operative pain, pain associated with malignant and non-malignant diseases), and neuropathic pain.

M6G.HBr may be administered by any suitable route. Examples are as a solid formulation (e.g. for oral, dry powder inhalation), as a solution formulation (e.g. intravenous (including infusion for PCA), subcutaneous, intranasal, or sublingual), or as a transdermal formulation (e.g. by simple diffusion or by enhanced electrophoretic methods). Transdermal administration of pharmaceutically acceptable acid addition salts of M6G is described in US 5,705,186.

According to the invention there is also provided a pharmaceutical composition comprising an analgesically effective amount of M6G.HBr together with a pharmaceutically acceptable carrier, excipient, or diluent.

An analgesically effective amount of M6G.HBr will vary with the route of administration. A suitable dose is in the range of 1-200mg/70Kg, preferably in the range of 5-75mg/70Kg. Dosage for routes of administration where bio-availability is high (e.g. intravenous, subcutaneous, intranasal, sublingual) will be lower than for routes with low bio-availability (e.g. oral).

M6G.HBr may also be used for the symptomatic treatment of breathlessness in patients with advanced cancer. Any suitable route of administration may be used, but a preferred route is inhalation of nebulized M6G.HBr. The effect of administration of nebulized M6G is described by Quigley *et al* in *J. Pain Symptom Manage.*, Letters, Vol **23**, No.1 (2002), pages 7-9. A dosage of M6G.HBr effective for the treatment of breathlessness in a subject with advanced cancer will vary with the route of administration. A suitable dose is in the range of 1-200mg/70Kg, preferably in the range of 5-75mg/70Kg.

The following examples relate to the stability of M6G salts at room temperature, and methods of preparation of M6G

salts. Table 1 shows the stability data for the M6G salts tested, and Figure 1 shows the chemical structure of M6G and identified degradants.

Example 1 Stability of M6G salts at room temperature

Analytical investigation by HPLC:

Samples of the hydrochloride salt (M6G.HCl) (205-2056), the sulphate salt (M6G.H_2SO_4) (205-2060), and the hydrobromide salt (M6G.HBr) (205-2059) of M6G were stored at room temperature for almost 6 years and then analysed by HPLC. The results are shown in Table 1, together with the results of HPLC analysis of samples prepared under similar conditions a few months earlier.

Results:

M6G.HCl (205-2056): The content of M6G decreased to 69% (starting from ~82%). HN-67002 and HN-67003 (which are typically oxidation products) increased to 1.3% and 2.1% respectively. The content of HN-33177, a synthetic impurity of M6G, remained unchanged. However, there are 17 peaks present in the chromatogram that cannot be identified by retention time. The total of these impurities is 9.2 area %.

M6G.H_2SO_4 (205-2060): The content of M6G decreased to 63% (starting from ~77%). HN-67002 and HN-67003 increased to 1.1% and 1.8% respectively. The content of HN-33177 did not change. However, there are 13 peaks present in the chromatogram that cannot be identified by retention time. The total of these impurities is 10.7 area % with a dominant peak at 23.5 min (6.55 area %).

M6G.HBr (205-2059): The content of M6G did not decrease at all and the content of HN-67002 (0.5%) and HN-67003 (0.2%) is much lower than in the samples discussed above. There are

only 4 additional peaks present in the chromatogram. None of these are bigger than 0.4 area %. The result is superior to the two other salts tested.

Conclusion:

The hydrobromide salt of M6G shows very limited degradation and was not discoloured after storage for six years at room temperature compared to the free base and other salts investigated. Thus, the hydrobromide salt of M6G has improved stability at room temperature compared to the hydrochloride and sulphate salts of M6G.

Example 2 Preparation of hydrobromide and sulphate salts of M6G

Preparation of Q 3196 (M6G.HBr, 304-4428):
4.99g of M6G.$2H_20$ were dissolved in 11ml of Methanol and cooled to -15°C. 1.16ml of HBr (48% in water) was diluted with 0.85ml of Methanol and cooled to -15°C and added slowly to the solution of M6G. A clear, highly viscous, pale yellow solution was obtained. The solution was stirred for 5 minutes before 100ml 2-propanol (-15°C) were added. The product precipitated immediately. The slurry was stirred for 3.5 hours at -20°C, the crystals were filtered off, washed with 37.5ml cold 2-propanol (-20°C) and dried at room temperature in a high vacuum. The yield was 5.61g.

Preparation of Q 3195 (M6G.H_2SO_4, 304-4429):
5.02g of M6G.$2H_20$ were dissolved in 11ml of Methanol and cooled to -15°C. 0.35ml of H_2SO_4 (96%) was diluted with 0.85ml of Methanol and cooled to -15°C and added slowly to the solution of M6G. A clear, highly viscous, pale yellow solution was obtained. The solution was stirred for 5 minutes before 100ml 2-propanol (-15°C) were added. The product precipitated immediately. The slurry was stirred for 3.5 hours at -20°C, the crystals were filtered off,

washed with 37.5ml cold 2-propanol (-20°C) and dried at room temperature in a high vacuum. The yield was 5.36g.

Table 1: Stability Data of M6G-Salts Stored at Ambient Temperature

Salt	Batch	Elasped Time (years)	Assay M6G uncorr.	Assay M6G corr.	HN-67002	HN-75076	Morphine	HN-75083	HN-67003	HN-33177	Unknown related substances (sum area %)
Hydrochloride	205-2042	0	82.2	88.7	---	n.d.	n.d.	< 0.1	---	0.3	<0.1
	205-2056	6	69.3	74.8	1.3	n.d.	0.2	n.d.	2.1	0.2	9.2
Sulphate	205-2041	0	77.2	93.6	---	n.d.	n.d.	< 0.1	---	0.2	0.2
	205-2060	6	63.3	76.8	1.1	n.d.	0.2	n.d.	1.8	0.3	10.7
Hydrobromide	205-2045	0	77.2	90.7	---	n.d.	n.d.	< 0.1	---	0.3	< 0.1
	205-2059	6	81.9	96.3	0.5	n.d.	n.d.	n.d.	0.2	0.4	1.0
Free base	F12061	0	N/A	98.2	n.d.	n.d.	n.d.	n.d.	n.d.	0.7	<0.1
	F12061	5	N/A	81.2	n.d.	n.d.	0.3	n.d.	n.d.	0.8	11.8

n.d. not detectable
--- not investigated
M6G uncorr. content calculated as M6G base
M6G corr. content calculated as M6G derivative = M6G uncorr. x f
f = molecular weight (M6G-derivative) / molecular weight (M6G)

M6G:	461.47	f=1.0000
M6G.HCl:	497.93	f=1.0790
M6G.H_2SO_4:	559.55	f=1.2125
M6G.HBr:	542.39	f=1.1753

Claims

1. A hydrobromide salt of morphine-6-β-D-glucuronide (M6G.HBr).

2. A pharmaceutical composition comprising an analgesically effective amount of M6G.HBr together with a pharmaceutically acceptable carrier, excipient, or diluent.

3. A pharmaceutical composition comprising an amount of M6G.HBr effective for the treatment of breathlessness in a subject with advanced cancer, together with a pharmaceutically acceptable carrier, excipient, or diluent.

4. M6G.HBr for use as a medicament.

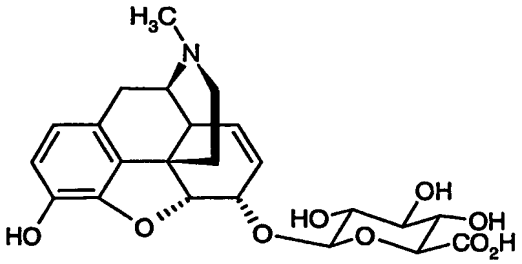
5. Use of M6G.HBr in the manufacture of a medicament for the treatment of pain.

6. Use of M6G.HBr in the manufacture of a medicament for the treatment of breathlessness in a subject with advanced cancer.

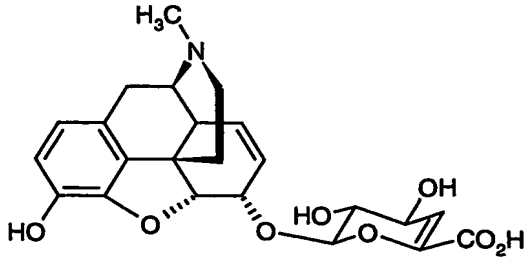
7. A method of treating pain which comprises administering a subject with an analgesically effective amount of M6G.HBr.

8. A method of treating breathlessness in a subject with advanced cancer which comprises administering the subject with an amount of M6G.HBr which is effective for reducing breathlessness.

Figure 1 Structure of M6G and Identified Related Substances



Morphine-6-ß-D-glucuronide (M6G)



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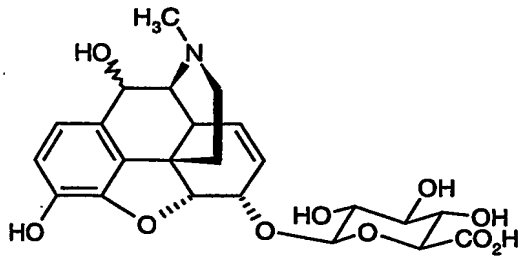

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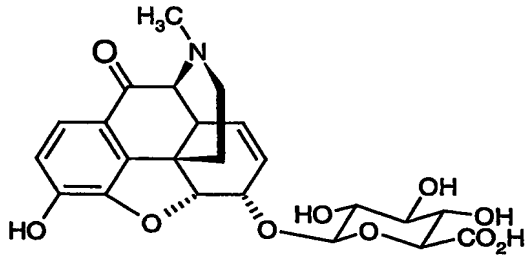
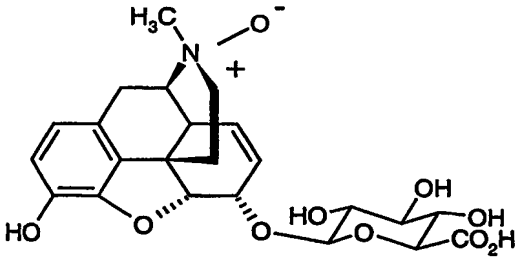
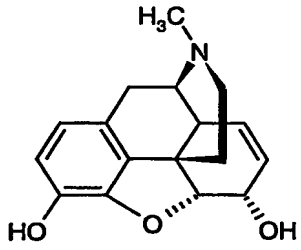


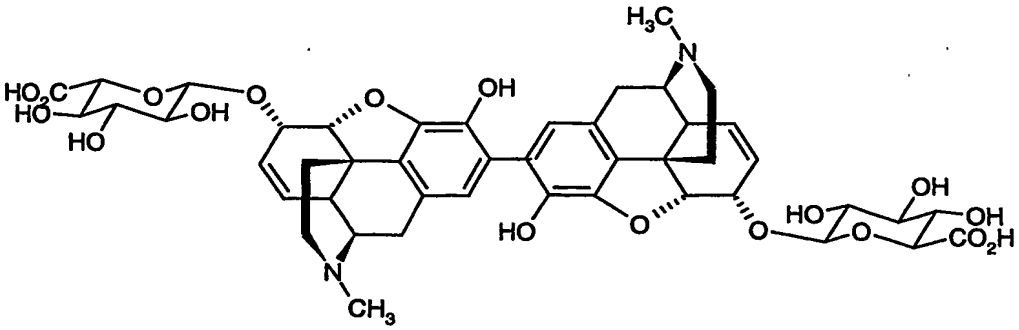
HN-67003



HN-75076



Morphine



HN-75083